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RESEARCH ARTICLE

Impact of appropriate antimicrobial therapy on survival in patients with *Acinetobacter baumannii*-associated infections

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ABSTRACT

Objective: To assess the impact of inappropriate antimicrobial treatment on the 30-day mortality in patients with *Acinetobacter baumannii* associated infections.

Methods: 87 patients with nosocomial infections caused by *A. baumannii* were included in the study. Among them 39 patients had favorable outcome, while 48 patients died within 30 days after pathogen isolation. In order to assess the impact of antimicrobial therapy on outcomes, the cases with appropriate antimicrobial treatment from both studied groups were compared with the cases in which patient's received inappropriate therapy. The Chi-square or Z-test was used to assess differences in categorical variables. Continuous variables were compared using the Mann-Whitney test.

Results: Among patients with favorable outcomes four people received appropriate empirical antimicrobial treatment, while in the other group only three patients. The odds ratio was 1.7 (95% CI 0.4-8.2; p=0.77). Appropriate antimicrobial agents were administered as a part of causal treatment to 27 patients who survived and to 11 patients who died within 30 days after pathogen isolation. The odds ratio was 6.7 (95% CI 2.6-17.3; p<0.001).

Conclusion: Our study has revealed that appropriate causal antimicrobial therapy decreases 30-day mortality rate in patients with nosocomial infections caused by *A. baumannii* . *J Microbiol Infect Dis 2013;3(4): 163-168*

Key words: *Acinetobacter baumannii*, mortality, antimicrobial therapy, nosocomial infections

Acinetobacter baumannii ilişkili enfeksiyonları olan hastalarda uygun antimikrobiyal tedavinin sağkalım üzerine etkisi

ÖZET

Amaç: *Acinetobacter baumannii* ilişkili enfeksiyonları olan hastalarda uygunsuz antimikrobiyal tedavinin 30 günlük mortaliteye etkisini değerlendirmek

Yöntemler: *A. baumannii* 'nin neden olduğu 87 hastane enfeksiyonlu hasta çalışmaya dahil edildi. Hastalardan 39'unda olumlu sonuç alınırken 48 hasta patojen izolasyondan sonraki 30 gün içinde öldü. Antimikrobiyal tedavinin akıbet üzerine etkisini değerlendirmek amacıyla, çalışılan gruplardan uygun antimikrobiyal tedavi ile uygunsuz tedavi alan hastalar karşılaştırıldı. Kategorik değişkenlerin farklılıklarını değerlendirmek için Ki-kare veya Z-testi kullanıldı. Sürekli değişkenler Mann-Whitney testi ile karşılaştırıldı.

Bulgular: Olumlu sonuçları olan hastalardan sadece dört kişi uygun ampirik antibiyotik tedavisi alırken diğer grupta bu yalnız üç hastaydı. Odds oranı 1,7 (% 95 CI 0,4-8,2, p=0,77) idi. Temel tedavinin bir parçası olarak uygun antimikrobiyal ajanlar uygulanarak tedavi verilen 27 hasta yaşarken, patojen izolasyondan sonra 30 gün içinde 11 hasta öldü. Odds oranı 6,7 (% 95 CI 2,6-17,3; p <0.001) idi.

Sonuç: Bizim çalışmamız; nedene yönelik uygun antibiyotik tedavisinin *A. baumannii*'ye bağlı hastane enfeksiyonları olan hastalarda 30 günlük mortalite oranını azalttığını ortaya koymuştur.

Anahtar kelimeler: *Acinetobacter baumannii*, mortalite, antimikrobial tedavi, nozokomiyal infeksion

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INTRODUCTION

In Europe more than 2 million of hospitalized patients acquire nosocomial infections each year, resulting in around 175 000 deaths per year.[1] Virtually every microorganism can cause infection in hospitalized patients, but among bacteria *Pseudomonas aeruginosa*, *Enterobacteriaceae spp*., *Acinetobacter spp*., *Staphylococcus aureus* and *Enterococcus spp*. take the leading positions.[2-4] *A. baumannii* (genospecies 2) has proven to be the most clinically important species within the genus.[5,6] In the last 20 years *A. baumannii* has grown into a large clinical challenge, a fact primarily attributed to common presence of resistance to almost all antimicrobial agents, including carbapenems and occasionally polymyxins; and the worldwide expansion of hospital areas.[7,8] The ability of *A. baumannii* to survive for extended periods on dry and wet environmental surfaces is notorious and is likely important for circulation and transmission within the health care setting.[9] The majority of *A. baumannii* -associated infections occur in intensive care units (ICU), the others - in oncological, neurosurgical, surgical, haematological and burn departments.[6,8,10] It can cause pneumonia (particularly, ventilator-associated pneumonia), bloodstream infections, urinary tract infections, skin and soft tissue infections, surgical site infections, meningitis, ventriculitis, ostheomyelitis, and intraabdominal infections.[6,8,10-12] *A. baumannii* causes infections mainly in severe immunocompromised patients.[6,11] The typical characteristics of affected patients include advanced age, presence of serious underlying diseases, immune suppression, major trauma or born injuries, invasive procedures during hospitalization, presence of indwelling catheters, performance of mechanical ventilation, as well as extended hospital stay and previous administration of broad-spectrum antibiotics.[6] Taking into consideration the above mentioned patients' features it becomes well understanding that attributable mortality related to this microorganism has been difficult to assess. That is why, some authors questioned the pathogenicity of the microorganism, making in this way discordance in the literature regarding the role of *A. baumannii* for lethal outcomes in these patients.[13-18]

The aim of this study was to assess the impact of inappropriate antimicrobial treatment on the 30-day mortality in patients with *A. baumannii* -associated infections.

METHODS

This retrospective study was performed at nine hospitals including seven multi-field hospitals and two specialized (Cardiology and Traumatology) medical centers located in Minsk (Belarus), whose capacities vary from 450 to 1050 beds. The study was approved by the ethical committee and conducted in accordance with its guidelines. Patients were enrolled in the study during the two-year period between December 2008 and November 2010.

All patients at the age of eighteen or older with nosocomial infections caused by *A. baumannii* were enrolled in the study. An infection was defined as nosocomial if the onset of signs and symptoms were on or after the third day of the admission, or were present at the admission or became apparent before the third day, but the patient had been discharged from a hospital less than thirty days before admission. When *A. baumannii* was consecutively isolated as a single pathogen from usually sterile sites or from non-sterile clinical material at concentration $>10^5$ CFU/ml, a case was considered to be etiologically confirmed.

Pathogen identification was performed initially in the local microbiological laboratory using VITEK® II automated microbial identification system (BioMerieux, France) and then confirmed in the reference center (Institute of Antimicrobial Chemotherapy, Smolensk, Russian Federation) using MALDI-TOF (Matrix Assisted Laser Desorption Ionization-Time of Flight) Mass Spectrometry method (MALDI Biotyper®, Bruker Corporation, USA).

Antimicrobial susceptibility testing was performed by agar-microdilution method. The results were interpreted according to the guidelines of the Clinical and Laboratory Standards Institute (CLSI, USA).[19] Intermediately susceptible isolates were regarded as resistant. The control strains *P. aeruginosa* ATCC® 27853, E. coli ATCC® 25922 and 35218, were tested simultaneously with the studied isolates for quality assurance purposes.

The measured outcome was a patient's death within thirty days after *A. baumannii* isolation from the clinical material. In order to assess the antimicrobial therapy impact on the outcome the odds ratio model was used. Antimicrobial therapy was considered to be appropriate, if the set of administered antibiotics included at least one antibiotic that was active in vitro against isolated strain of *A. baumannii* and if the route of administration and the dosage were appropriate. Empirical antimicrobial therapy was defined as administration of antibiotic before *A. baumannii* isolation, while causal antimicrobial therapy - as antibiotic administration after *A. baumannii* isolation.

Data were analyzed using Statistica® software v.6.0 (StatSoft Inc., USA). The Chi-squared ($\chi 2$) or

the Z-test was used to assess differences in categorical variables, as appropriate. Continuous variables were compared using the Student's t test or the Mann-Whitney test. The Shapiro-Wilk's test was used to assess normality. A two-sided P value of less than 0.05 was considered to indicate statistical significance.

RESULTS

During the study period, 87 eligible patients were identified. The vast majority (77%) of them were hospitalized to intensive care units; the others - to surgical (13.8%), therapeutical (6.9%) and hematological (2.3%) departments. Among isolated *A. baumannii* strains 93.1% were multidrug-resistant (i.e. non-susceptible to at least one agent in 3 or more antimicrobial categories). A substantial number of isolates were resistant to imipenem (51.7%) and meropenem (58.6%), sulbactam (34.5%), however all studied *Acinetobacteria* were susceptible to colistin.

Among them 39 patients survived or had significant improvement of their health status (favorable outcome) and 48 patients died (unfavorable outcome) within thirty days after *A. baumannii* isolation. Thus within 30 days after pathogen isolation the overall mortality rate among patients with *A. baumannii*-associated infections included in the study was 55.2%. Both groups were comparable in age, sex, the weight of ICU-hospitalized patients and the proportion of isolated multidrug-resistant (MDR) *A. baumannii* as shown in the Table 1. Patient age distribution within every studied group is represented in the Figure 1.

Table 1. Characteristics of the patients with nosocomial *A. baumannii*-associated infections according to the outcomes on Day 30 after pathogen isolation

Variables	Favorable outcome (n=39)	Unfavorable outcome (n=48)	p value
Mean ± SD (years old)	50.9 ± 5.6	57.2 ± 3.8	0.06
Gender, Male (%)	25 (64.1%)	35 (72.9%)	0.52
Weight of ICU-hospitalized patients	27 (69.2%)	40 (83.3%)	0.19
Isolation of MDR A. baumannii	35 (89.7%)	46 (95.8%)	0.49

SD=standard deviation; ICU=intensive care unit; MDR=multidrug-resistant

Among patients with favorable outcomes, 4 persons (10.3%) received appropriate empirical antimicrobial treatment, while in the other group - only 3 patients (6.3%). The odds ratio was 1.7 (95% confidence interval (CI), 0.4-8.2) but the difference was not significant (p = 0.77).

At the same time, appropriate antimicrobial agents were administered as a part of causal treatment to 27 patients (69.2%) who survived and to 11 patients (22.9%) who died within 30 days after pathogen isolation. The odds ratio was 6.7 (95% CI 2.6-17.3), the difference reached statistical significance (p<0.001).

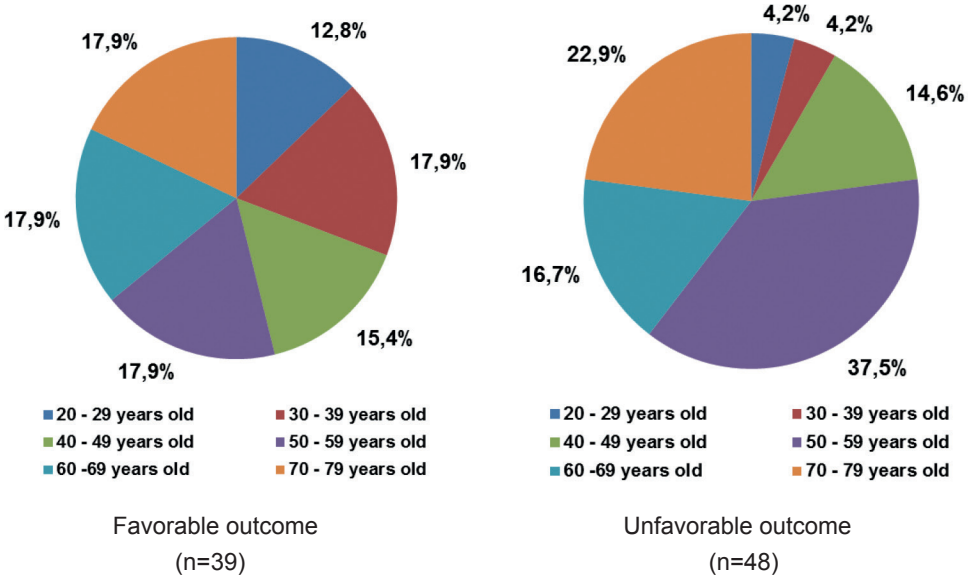

Fig 1. Age distribution of the patients with nosocomial *Acinetobacter baumannii*-associated infections within studied groups.

DISCUSSION

The main finding of this study is that administration of inappropriate antimicrobial therapy significantly increases the 30-day mortality rate in patients with *A. baumannii*-associated infections. Based on these data, it is clear that *A. baumannii* contributes to increased mortality rate. Thus, the results of the present study confirm that *A. baumannii* is a real pathogen and infections caused by this microorganism are associated with increased mortality. In accordance with our findings, Joung et al. confirmed that inappropriate definitive antimicrobial therapy (odds ratio (OR) 3.05; 95% CI: 1.05-8.86; P=0.04) and Acute Physiology and Chronic Health Evaluation (APACHE) II score ≥20 (OR 4.27; 95% CI: 1.57-11.64; P=0.005) were independent factors associated with a high mortality in 116 patients with clinically significant *Acinetobacter* hospital acquired pneumonia 20). In the other study performed by the authors from China APACHE II score >20 at disease onset (OR 3.02; 95%CI: 1.3-7.0; P=0.01), presence of chronic respiratory disease (OR 3.17; 95%CI: 1.38-7.28: P=0.01), infections with additional pathogen (OR 9.01; 95%CI: 4.0-21.02; P<0.001), and inappropriate antibiotic treatment (OR 6.92; 95%CI: 2.95-16.22: P<0.001) were independently associated with 28-day mortality in patients with nosocomial pneumonia caused by carbapenem-resistant *A. baumannii*.[21] Lee et al. reported that appropriate antimicrobial therapy was independently associated with reduced mortality in patients with *A. baumannii* bacteremia (OR 0.22; 95% CI, 0.01-0.50; P <0.001), but the benefit of appropriate therapy was limited to patients with high APACHE II scores (OR for patients with scores >25 and ≤ 35, 0.16; 95% CI, 0.07-0.37; OR for those with scores >35, 0.06; 95% CI, 0.01-0.25) 22. In Thailand a retrospective study of 110 patients with carbapenem-resistant *A. baumannii* nosocomial infections demonstrated that renal impairment, bloodstream infection, and inappropriate antimicrobial regimen were independent predictors of treatment failure and poor treatment outcomes.[23] It is important to note that according to the data from some clinical studies, resistance to carbapenems by itself has no impact on mortality rates in patients with *A. baumannii* infections.[24-26] And finally, a systematic review of matched case-control and cohort studies examining the mortality that is attributable to infection or colonization with *A. baumannii* revealed that statistically significant higher mortality was associated with *A. baumannii* infection or colonization.[16] In the hospital and in the intensive care units the attributable mortalities of patients with *A. baumannii* infection ranged from 7.8% to 23% and from 10% to 43% respectively.[9,16,17]

However, Eberly et al. stated that *A. baumannii* infection, including multidrug-resistant strains, has inconclusive impact on mortality in a cohort of trauma patients. The in-hospital mortality was higher in the pathogen group (16% vs. 13%; p=0.67), but the difference was not significant. At the same time *A. baumannii* infection was associated with a longer intensive care unit stay (median, (range), 28 (7-181) days vs. 17 (2-130) days, respectively; p=0.05) and a higher rate of ARDS and acute liver failure (35% vs. 15%; p = 0.02 and 26% vs. 10%; p = 0.04) when compared to controls.13 In Belgian retrospective matched cohort study in critically ill patients *A. baumannii* bacteremia was associated only with more severe hemodynamic instability, longer ICU stay, and longer length of ventilator dependence, but not associated with a significantly increased mortality rate (42.2% vs. 34.4% when compared to control group).[15]

On the contrary to some other studies, we did not confirm the influence of inappropriate empirical therapy on clinical outcomes in those patients.[18,27,28] Erbay et al. reported that significant independent risk factors for mortality in patients with *A. baumannii* bacteremia were delayed appropriate treatment (hazard ratio (HR)=2.4, 95% CI)1.3-4.2; p=0.004), development of septic shock (HR=2.6, 95% CI 1.4-4.8; p=0.004), age>65 years (HR=2.1, 95% CI 1.2-3.7; p=0.007) and mechanical ventilation (HR=3.3, 95% CI 1.5-7.4; p=0.003) 18. In the other study performed by Taiwan authors prolonged ventilation days (odds ratio=3.4; 95% CI 1.7-6.1; p=0.01) and inappropriate empiric antibiotic therapy within 48 hours (odds ratio=7.9; 95% CI: 3.9-9.8; p=0.02) were independent factors that predicted the 30-day mortality from nosocomial *A. baumannii* infections in chronically ventilated patients.[27] In their study Lee et al. found that the 30-day crude mortality rate was higher among patients received inappropriate empirical antimicrobial therapy than it was among patients initially treated by appropriate (in vitro active) antibiotic regimens (32/63, 50.8% vs. 21/67, 31.3%; p=0.032). Another interesting finding from their study was observation that the patients with empirical combination therapy had a lower mortality rate (adjusted odds ratio 0.31; 95% CI: 0.15-0.72; p=0.006).[28]

Reported in our research overall mortality rate of 55.2% is rather high but it correlates with the data received from other studies. The crude mortality rate in patients with *A. baumannii*-associated in-

fections varies from 14% to 60% depending on the study.[8,29-31]

This study has limitations and strengths. The limitations include a small sample size and retrospective design. The strengths include the accurate pathogen identification using MALDI-TOF-mass-spectrometry method, and the clear definition of nosocomial origin of infection in the included patients based on clinical interpretation of every case.

In conclusion, we have found out that inappropriate antimicrobial therapy increased 30-day mortality rate in patients with nosocomial infections caused by *A. baumannii*, thus confirming the statement that *A. baumannii* is a real pathogen but not a witness of the lethal outcome. Taking into consideration, that the majority of hospital isolates of *A. baumannii* was multidrug-resistant and also the differences in the pathogen resistance phenotypes between different countries, cities and even hospitals, it is crucial for adequate anti-*Acinetobacter* therapy to use local clinical and microbiological data.

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